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STUDIES ON THE PANCREATITIS IN A MOUSE HEPATITIS VIRUS (MHV-3) INFECTION*

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Mouse hepatitis group of viruses (MHV) have a common pathogenic property, namely, of producing hepatic lesions in mice[1)2)3)4)]. The pathology of the hepatitis caused by these viruses has been extensively studied as an experimental model for the study of human viral hepatitis[5)6)7)8)9)10)11)12)13)14)]. On the contrary, few studies have been made on lesions in other organs and tissues in MHV infections [4)9)15)]. Hirano and Ruebner pointed out that a strain of mouse hepatitis virus (MHV-3) produced widespread severe necrosis of lymphoid follicles in the spleen, lymph nodes and Peyer's patches which was comparable to the hepatic lesions in severity and probably in importance[16)]. Further studies revealed another pathogenic property of this virus, namely, it produced pancreatitis with accompanying fat necrosis in certain strains of mice. This communication deals with these recent findings in the pathology of MHV-3 infection.

MATERIALS AND METHODS

Animals

Four strains of mice, CFW, CD-1, DBA/2 and BALB/C, 50 animals each were employed. All of them were weanling females, three to four weeks old and nine to 15 gm in body weight. They were caged in groups of ten and were allowed free access to food and water.

virus

The MHV-3 strain of mouse hepatitis virus[4)] was used in the form of a suspension of liver from infected animals diluted 1 : 1,000 in Gey's solution. Each animal was injected with 0.1 ml of the virus suspension intraperitoneally. This dose was at least ten times as high as LD_{100}. In order to observe the maximal effect of the virus, the animals were allowed to die spontaneously and the liver, spleen, thymus, lymph nodes and the pancreas were usually examined by routine histological methods.

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RESULTS

Mortality

All the animals injected with the virus eventually died regardless of the strains. The great majority of them died on the fourth and fifth day of infection while some died on the third as well as on the sixth or seventh day. No further attempts were made of determining strain difference in susceptibility to the virus.

Hepatic lesions

The liver became diffusely pale, greyish and somewhat swollen in all the animals. Histological examination revealed numerous foci of coagulative necrosis which varied in size and were often coalescent as has already been described in detail[9)14)]. No appreciable strain difference was noted in the extent of the lesion.

Lymphoid lesions

The normal lymphoid follicles in the spleen of these mice were composed of densely packed small or medium-sized lymphocytes. They could be divided

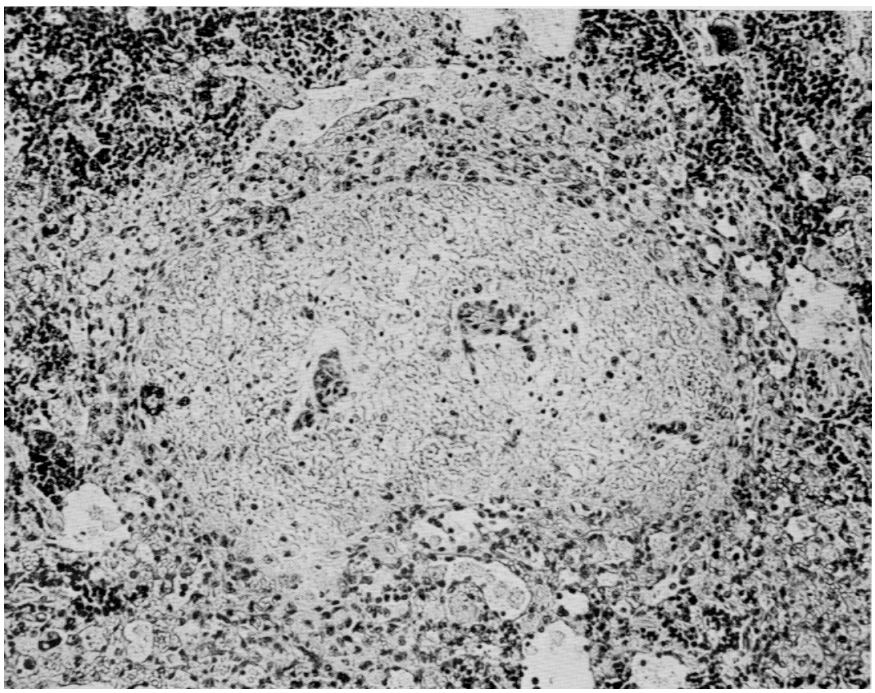

FIG. 1. The spleen of a DBA/2 mouse 72 hours after MHV-3 infection. Note complete disappearance of a lymphoid follicle. Fbirinoid substance is deposited at the necrotic area. The marginal zone of this follicle is depleted in its lymphocytes. Hematoxylin and eosin staining; ×175.

into two parts; the large central area named true follicle and the surrounding narrow zone called marginal zone. Between these two areas is situated a vascular structure named the marginal sinus[16]. The full-blown lesion in MHV-3 infection was virtual disappearance of the true follicles (Fig. 1). In the earlier stage of the disease, the necrotic lesions were localized just inside the marginal sinus. The necrosis extended centripetally towards the central arteriole in a very regular way. Marked deposit of fibrinoid substance was localized at the round necrotic areas corresponding to the true follicles. In contrast to this, the marginal zones frequently remained intact. They sometimes showed considerable decrease in lymphocyte population but real necrosis of the marginal zones was not observed in any follicle.

The megakaryocytes in the red pulp manifested a degenerative change: the nuclei became pyknotic and the cytoplasm was condensed. No other remarkable changes were noted in the red pulp. Lymphoid follicles in lymph nodes as well as Peyer's patches of the intestine were shown to have fallen into necrosis which was essentially similar to that observed in the spleen.

All these changes in the lymphoid tissue were common to all the four strains of mice and no noticeable strain difference was present in this respect.

Fat necrosis

All the DBA/2 mice showed numerous, small, chalky-white spots scattered all over the peritoneal surface. The spots were also observed outside the peritoneal cavity such as the subcutaneous tissue of the abdominal wall. The same lesions were observed in all the BALB/C mice in a somewhat less marked

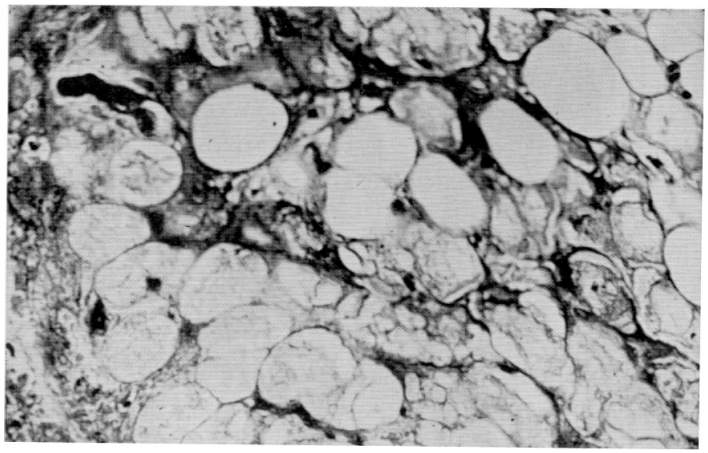

FIG. 2. Microscopic picture of a white spot in the peritoneal cavity of a DBA/2 mouse 72 hours after NHV-3 infection. Most of the fat cells have been transformed into shadowy outlines of cell membranes filled with pink, granular, opaque precipitate. Note the absence of inflammatory cell infiltrate. Hematoxylin and eosin staining; ×250.

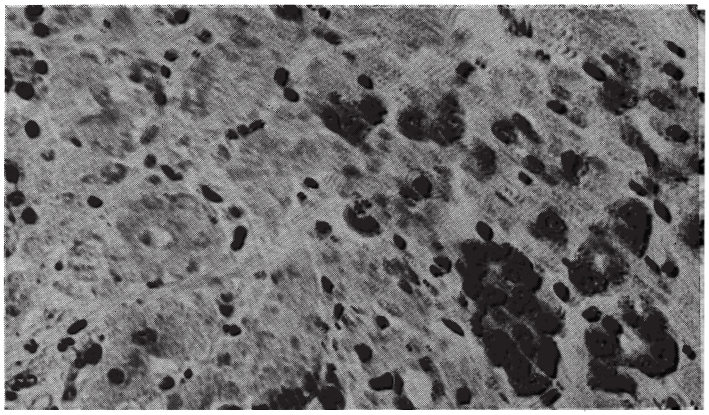

FIG. 3. The pancreas of a moribund DBA/2 mouse 72 hours after MHV-3 infection. Massive necrosis of granular coagulative type involves many pancreatic acini. Surviving acini are scattered. Inflammatory cell infiltrate is hardly present. Hematoxylin and eosin staining; ×400.

degree. None of the CFW mice and CD-1 mice, on the contrary, were shown to have such lesions. Microscopic examination of the spots revealed that vacuolated fat cells were transformed into shadowy outlines of cell membranes filled with pink, granular, opaque precipitate (Fig. 2). Mild inflammatory cell infiltrate was observed at the periphery but not in the central area of these lesions.

Pancreas

Grossly, all the DBA/2 mice and BALB/C mice had a whitish, remarkably hardened portion localized at the tip of the pancreatic lobe which was adjacent to the stomach. The rest of the pancreas did not show any appreciable change both in color and consistency. None of the CFW mice and CD-1 mice, on the contrary, were noted to have such lesions. Microscopic examination of the whitish, hardened portion revealed various-sized foci of granular coagulative necrosis of pancreatic acini (Fig. 3). Inflammatory cell infiltrate was confined to the margins of the necrotic foci.

DISCUSSION

These studies clearly showed that MHV-3 produces not only hepatitis but also lymphoid necrosis and, in some strains, pancreatic necrosis. Among the three major pathological changes in this viral disease, the pancreatic lesion has a unique feature; its incidence is entirely dependent on the strain of mice; all the DBA/2 and BALB/C mice developed the pancreatic lesion with accompanying fat necrosis while the evidences of pancreatitis were clearly absent in the CFW mice and CD-1 mice which showed severe hepatitis as well as lymphoid

necrosis. It is to be concluded, therefore, that the lesion of the pancreas is essentially different in its pathogenesis from that of the liver and the lymphoid tissue. It would not be possible to find that MHV-3 also produces pancreatitis, unless such strains of mice as DBA/2 or BALB/C were employed in the experiments. This seems to explain the reason why the pancreatic lesion in this infection has not been reported. In this connection, it will be interesting to see whether or not a high titer of the virus is present in the pancreas of the CFW and CD-1 mice which show no pancreatitis despite the severe lesions in the liver and the spleen.

The hepatitis and the lymphoid necrosis seem to accompany each other: all the mice which had extensive hepatic lesions were shown to have the lymphoid necrosis while those with lymphoid necrosis were always found to have severe hepatic lesions. On the other hand, the animals injected with sublethal doses of the virus developed neither the hepatitis nor the lymphoid necrosis[17]. These results seem to indicate that the development of either the hepatitis alone or the lymphoid necrosis alone does not occur. This does not mean, however, that there is a causal relation between these two lesions. The author demonstrated that it was possible to produce the hepatitis alone or, conversely, the lymphoid necrosis alone through treatment by chemicals[18)19)]. These results indicate that the lymphoid necrosis is not secondary to the hepatitis and vice versa. It was also shown that the titers of the virus in the liver and the spleen were approximately the same[18]. All these findings seem to suggest that multiplication of MHV-3 occurs equally both in the liver and the spleen, resulting in production of the lesions always in both organs.

A large question has arisen from these studies, namely, the definition of susceptibility of an animal to the virus. The susceptibility or resistence to a microorganism is defined at the level of an animal; when the target organ(s) of the virus is damaged by the virus, the animal as a whole is considered to be susceptible to the virus. This definition does not give a clear answer in the CFW and CD-1 mice infected with MHV-3. It seems that the susceptibility needs to be defined at the level of organs in this viral disease.

SUMMARY

A strain of mouse hepatitis virus (MHV-3) produced necrotic lesions in the pancreas in addition to fatal hepatitis and severe lymphoid necrosis in DBA/2 mice and BALB/C mice. The lesions consisted of scattered foci of granular, coagulative necrosis localized at the tip of the pancreatic lobe which was adjacent to the stomach. Numerous foci of fat necrosis were widely scattered in the peritoneal cavity and occasionally even in the subcutaneous tissue of the abdominal wall.

In contrast to this, no evidences of pancreatitis were noted in CFW mice and CD-1 mice, despite the development of the hepatitis and the lymphoid necrosis which were as severe as those in the DBA/2 and BALB/C mice.

These findings suggest that it is not sufficient to define susceptibility or resistence to this virus at the level of an animal; it needs to be defined at the level of an organ.

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